Improving Cardiopulmonary Bypass: Heparin-Coated Circuits

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Abstract: Heparin-coated circuits have been repeatedly proven to reduce the inflammatory response and foreign surface activation triggered upon initiation of cardiopulmonary bypass (CPB). In recent years, increasing numbers of studies are proving significant reductions in postoperative blood loss and transfusion requirements and improvements in clinical outcomes as a result of heparin-coated circuits. These results are promising steps in our efforts to improve CPB, as our patient population gets older and more complicated. JECT. 2003;35:312–316

Cardiopulmonary bypass (CPB) is continually changing and improving. Over the years, many new techniques and novel devices have been introduced, some embraced, others tested and discarded. Heparin-coated circuits have been available for many years, but few have embraced this technology for everyday use and the advantages it provides. While some of our colleagues have turned to off-pump coronary artery bypass grafting (CABG) as a way of avoiding CPB and its damaging effects, others have been looking for ways to improve CPB. Recent studies completed at Boston University have helped to prove that heparin-coated circuits are intrinsic to the concerted effort to improve CPB. The key to heparin-coated circuits and to improving CPB is to not only change the circuits, but to reconsider the techniques and the way we think about all aspects of CPB.

BIOCOMPATIBILITY

Moments after the initiation of CPB, foreign surface activation causes the inflammatory response to begin. The coagulation, fibrinolytic, complement, and kallikrein cascades are all activated to some degree, as well as the leukocytes, platelets and endothelial cells (1,2). This activation corresponds to the postoperative bleeding and morbidity associated with CPB.

The biocompatibility of heparin-coated circuits provides some reduction in the activation of the inflammatory response, which in turn provides a number of benefits to the patient. Biocompatibility reduces foreign surface activation immediately upon initiation of bypass, which results in improved hemostasis, decreased thrombogenicity, and improved preservation of coagulation factors and platelet function in comparison to traditional circuits. The blunted inflammatory response is a result of decreased complement activation, decreased neutrophil activation, as well as a reduction in the activation of tumor necrosis factor (TNF) and the interleukins (3,4). One study completed in Norway experienced a 45% reduction in complement activation with heparin-coated circuits (5). These factors all contribute to a reduction in cardiac, renal, and pulmonary dysfunction following bypass.

CARMEDA AND DURAFLO COATINGS

There are two methods of heparin bonding currently available, Duraflo II (Baxter, Irvine, CA) and Carmeda (Medtronic, Minneapolis, MN). The Duraflo coating is a ionically bonded, unfragmented heparin complex. The Carmeda coating is a covalently bonded, fragmented heparin product providing long-term stability and more pronounced reduction in complement and granulocyte activation than the Duraflo product (6).

Several comparative studies have revealed significant advantages to choosing the Carmeda coating over the Duraflo coating in terms of reducing the degree of inflammatory response (3,4). This suggested a corresponding clinical advantage to using the Carmeda coating, but a recent study completed by Ovrum and colleagues in Norway studied 1336 patients and concluded that the two circuits have similar effectiveness in terms of outcomes, in fact the only difference in the study was a reduction in heparin requirements in the Duraflo group hypothesized to be due to leaching (6).

The recent introduction of heparin-coated cannulas, arterial filters, and other circuit elements within the past ten years have allowed a “tip to tip” heparin coating of the
entire CPB circuit. The current resurgence in heparin-coated technology is likely due to the availability of coatings and the added benefit and safety provided with the “tip to tip” heparin coating.

ADDITIONAL TECHNIQUES AVAILABLE TO IMPROVE CPB

Biocompatibility is essential to the improvement of CPB, but there are additional steps that the cardiac team must also embrace to further improve clinical outcomes and reduce costs. Cardiac teams should attempt to streamline their circuits and focus on changes that can reduce damage to the blood components and reduce activation of the inflammation process. Each step may not have a significant impact in its own right, but the combined technique is effective (7,8,9).

Reduction of blood to air interface with a closed CPB system is one effective method. By reducing shear stresses with the exclusive use of centrifugal pumps and large bore venous and directional arterial cannulas further steps can be made toward the reduction of foreign surface activation and blood damage.

Of primary importance and becoming increasingly recognized is the elimination or reduction of pump suction. Cardiotomy suction introduces proinflammatory and procoagulant factors and debris from the surgical field into systemic circulation, thereby increasing thrombin generation, inflammation, platelet activation, and neuronal injury. A recent study performed by Aldea and colleagues in Seattle, WA compared heparin-bonded circuits with cardiotomy suction to heparin-bonded circuits without cardiotomy suction (10). This study proved that the elimination of cardiotomy suction significantly reduced the markers for inflammation and platelet activation. (Presented by GS Aldea at the Western Thoracic Conference, San Diego, CA, June 20–24, 2001).

Low prime CPB with the use of retrograde autologous priming can reduce hemodilution and transfusion requirements (11). Routine use of epsilon aminocaproic acid (Amicar), an antifibrinolytic agent, results in decreased perioperative blood loss and transfusion requirements (9). Hypothermia also results in increased fibrinolysis suggesting that minimal cooling on bypass (34°C) could also benefit the patient.

Precise heparin and protamine titration with heparin dose response curves can reduce dosages in comparison to empiric calculations, thereby reducing the degree of postoperative platelet dysfunction and increased fibrinolysis associated with heparin and heparin-protamine complexes. Heparin’s influence on platelet dysfunction is a result of prolonged bleeding times and a reduction in the ability to product Thromboxane A2. Increased fibrinolysis results in increased plasma levels of plasmin and D-dimer which then go on to interfere with platelet aggregation further perpetuating the damage of heparin (12). In addition, attempting to reduce heparin levels during standard CABG patients can further benefit patients. The goal of low anticoagulation is to minimize heparin levels and thereby its damage to platelets and fibrin while adequately suppressing thrombin to maintain the safety of CPB. The corresponding reduction in protamine levels is also a benefit, as protamine is known to cause hemodynamic instability, hypersensitivity and platelet activation (13).

EFFECTS ON CLINICAL OUTCOMES

Implementation of these combined techniques was first studied by Gabriel Aldea, MD, Patrick Treanor, CCP, and colleagues at Boston University. The study included 404 patients undergoing CABG, excluding reoperations and cath lab emergencies. Standard transfusion thresholds and clinical pathways leading to extubation, SICU and hospital discharge were followed for all patients. The patients were randomized into two groups, one using a traditional non-heparin-bonded circuit (NHBC) with an activated clotting time ACT >480, the other using the heparin-bonded circuit (HBC) excluding pump suction with an ACT >280. The results of this study revealed a 43% reduction in transfusions in the HBC group, and 32% reduction in ventilatory support and SICU stay. (Figures 1 and 2) The clinical outcomes were significantly improved in the HBC group in terms of postoperative MI, pulmonary function, and inotropic support (7,9) (Figure 3). These results revealed a definitive benefit to the new techniques and heparin-bonded circuits but failed to delineate which aspects were the most advantageous. The study supports the idea that a concerted approach to improve CPB is effective, currently available, and cost effective.

REDUCED ANTICOAGULATION

After the first results utilizing reduced anticoagulation were published, many questions began to arise regarding the benefit of the low anticoagulation protocol in compari-

![Figure 1. Homologous units transfused per patient.](http://example.com/figure1.png)

\* p < 0.03 (43% reduction)
son to higher heparin levels. To what level should surgeons and perfusionists be concerned about thromboembolic complications and thrombin generation during CPB as a result of the low anticoagulation protocol?

Previous studies with low anticoagulation in Europe had shown no clinical evidence of thrombogenicity or clot in the CPB circuit. However, one study did reveal a slight elevation of the thrombotic markers, thrombin antithrombin complex, and prothrombin fragment 1.2, during bypass above the noncoated circuit with full anticoagulation levels indicating continued thrombin production during bypass (13). These measurements were not significant, but they did contribute to the concern over the safety of low anticoagulation.

In efforts to quell concerns regarding the low anticoagulation protocol (LAP) with HBC circuits, a second study was performed by Dr. Aldea and colleagues at Boston University. This study compared HBC’s with a low heparin protocol and ACT >250 to full heparinization and an ACT >450 (Figure 4). The study included 260 randomized CABG patients excluding reoperations and cath lab emergencies. Standard surgical techniques and equipment were used in this study including the elimination of pump suction, and standard transfusion thresholds and clinical pathways were maintained. The results of this study revealed a 54% reduction in initial heparin dose and protamine dose in the low anticoagulation protocol (LAP) in comparison to the full anticoagulation protocol (FAP) group (Figures 5 and 6). The LAP group also showed a 54% reduction in transfusions as well as a significant reduction in length of stay and thrombo-embolic complications such as MI, cardiovascular accident (CVA),Transient ischemic attack (TIA), and vascular complications (8) (Figure 7). Therefore, the benefits of lower heparin levels combined with the techniques advocated by Aldea appear to extend beyond the decreased post bypass platelet dysfunction and fibrinolysis previously demonstrated.

SAFETY

The safety of heparin-coated circuits has been repeatedly proven (7,13–15). Published studies have revealed no incidents or concerns during bypass regarding patient safety. One study performed in Switzerland weighed oxygenators and venous reservoirs following CPB and found no differences in weight between high and low anticoagulated groups (14). In addition, a study by Dr. Aldea at Boston University included testing to prove the safety of low anticoagulation. Electromagnetic analysis of the arterial filter was performed from 40 cases of the two groups (LAP, FAP). The results revealed an 81% reduction in arterial filter debris in the low anticoagulation group compared to the full anticoagulation group (9) (Figure 8). Further, transcranial Doppler analysis performed in 40 patients of the low and high anticoagulation groups showed that the majority of emboli were measured with manipulation of the aorta during cannulation and cross clamping, and not during initiation and removal from CPB (8) (Figure 9). These results prove the safety of low anticoagulation for standard low risk CABG patients.

REOPERATIONS, VALVES AND HIGH RISK PATIENTS

While the vast majority of studies performed thus far have focused on primary CABG patients, the techniques and heparin coatings can provide similar or even improved
benefit to other patients. Full anticoagulation is recommended for high-risk patients, reoperations, valves, circulatory arrest cases, or any case where prolonged periods of low flow are encountered. The group in Norway noted clots in the cardiotomy reservoir after two reoperation CABG's and subsequently converted to full anticoagulation in these cases (6). The groups in Seattle and Boston increase heparin levels with the addition of a cardiotomy reservoir and suction to the circuit.

As greater numbers of high-risk patients are included in studies, we expect to see even greater benefits in terms of clinical outcomes with heparin-coated circuits (16). A multicenter study in Italy by Dr. Ranucci and colleagues revealed a decrease in lung and renal dysfunction for a subset of patients with COPD and diabetes respectively (17). A study focused on emergent CABG's at Boston University found significant reductions in the incidence of perioperative MI, postoperative inotropic requirements, pulmonary complications and atrial fibrillation with the use of heparin-bonded circuits, reduced anticoagulation (ACT > 280) and elimination of cardiotomy suction (18).

Cardiotomy suction may be required on difficult reoperations, valves, and other cases, but with minimal use and attempts to reduce the blood to air interface, significant improvements can be made to all aspects of CPB. The key to implementing these distinct changes to technique and improving outcomes is cooperation between surgeons, perfusionists, anesthesiologists and all members of the cardiac team. The learning curve may take some time, but in the end, bypass can be safer for patients with fewer transfusions, fewer complications and shorter hospital stays (Figures 10 and 11).

CONCLUSIONS

With these studies completed, the focus on heparin-bonded circuits is stronger than ever. These studies show that heparin-coated circuits, combined with these new techniques, can result in significant improvements in clinical outcomes. Regardless of efforts to avoid CPB in some cases, CPB will continue to be necessary for aortic repairs, valves, and congenital defects, so it remains crucial to con-
continue to find ways to improve CPB and make it safer. Future innovation in the areas of biocompatibility with new third generation coatings and drug therapies that can preserve platelets and/or block inflammation are all potential keys to the continued success of CPB.

REFERENCES